Quantification Issues in Bolus-Tracking Perfusion MRI

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Introduction

Bolus-tracking perfusion MRI is based on the monitoring of the first passage of a bolus of contrast agent through the brain tissue and a brain-feeding artery. The contrast agent is injected rapidly in the antecubital vein in the patients arm by means of an MR-compatible power injector. This bolus of contrast agent is pushed in the direction of the heart by means of a saline flush. Continuous dynamic scanning with a typical temporal resolution of approximately 1-2 second is used to monitor the passage of the contrast agent through the brain tissue and a brain-feeding artery. The change in MR signal is hereafter converted into the concentration of contrast agent based on the physical properties of the contrast agent. The time evolution of the concentration of contrast agent in the brain-feeding artery is called the arterial input function. Deconvolving the passage through the brain tissue with the arterial input function, results in the tissue response function. Based on the theory of tracer kinetics, perfusion parameters are calculated from this tissue response function. To achieve quantitative measures of perfusion, all these different aspects should be considered.

Contrast agent properties-artery

Spin echo sequences

Spin echo sequences are especially favourable for perfusion MRI, since it is more weighted to the microvasculature than gradient echoes sequence (2). However, it can only measure the shape of the arterial input function (3). This is because the input function is measured in the vicinity of the artery and is therefore highly dependent on the exact location with respect to the artery. It has been shown in experiments in dogs that the observed signal changes are proportional to the concentration of contrast agent (4).

Gradient echo sequences

The presence of contrast agent in an artery influences the MR-signal in two ways:

1. The amplitude of the MR-signal will decrease, since the contrast agent will create field inhomogeneities. The presence of the red blood cells leads to compartmentalization of the contrast agent, that results in a non-linear relationship between the concentration of contrast agent and the ΔR_2^* (see Fig. 1) (1,5). This non-linear relationship is frequently neglected and a linear approximation is used. However, neglecting this quadratic relation will affect quantitative measures of cerebral blood flow, volume and mean transit time. Most perfusion studies use this amplitude effect to measure the arterial input function.
2. Due to the different susceptibility of the contrast agent, the magnetic field inside the artery will change. This leads to phase changes (see Fig. 1) (6). The angle of the artery with respect

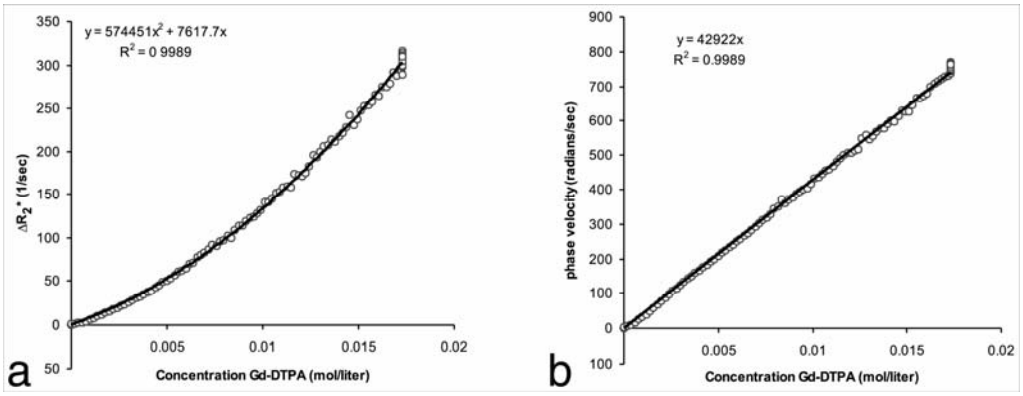

Figure 1. Changes in MR signal versus contrast agent concentration as measured in flowing, fully oxygenated blood at body temperature ((1)). **a:** ΔR_2^*. **b:** phase velocity ($\Delta\theta/\Delta TE$).

to the main magnetic field determines the proportionality constant between the intravascular phase and the concentration of contrast agent. For an artery oriented at 54.7° (the magic angle) no phase changes will occur within the artery. Measurements of phase changes in a tube parallel to the main magnetic field have shown a linear relation between the phase change and the concentration of contrast agent independent of the hematocrit of blood (5). Because of this insensitivity to hematocrit differences and the higher SNR of phase measurements, phase changes are also used to quantify the concentration contrast agent in the artery(7)

Arterial input function measurements

Because spin echo sequences are not capable of measuring the arterial input function quantitatively, gradient echo sequences are used when absolute quantification is required. However, it is important to realize that the resolution of a typical sequence is too low to find a voxel that is exclusively sensitive to arterial blood since partial volume effects will occur. Two situations can be differentiated when describing partial volume effects of input function measurements with gradient echo sequences:

Artery parallel to the main magnetic field

When an artery is oriented parallel to the main magnetic field, the magnetic field changes are limited to the inside of the artery. This implies that signal from tissue surrounding the artery is not influenced by the presence of contrast agent in the artery. The total signal of a voxel with partial volume effects can therefore be described by the complex sum of a stationary signal component from tissue and dynamically changing signal from the blood. A change in the concentration of contrast agent will affect both the phase and the amplitude of the blood signal. During a bolus passage, the complex blood signal will therefore traverse a spiral-like trajectory, originating from the quadratic change in ΔR_2^* (that is a decrease in amplitude) and a linear phase change (see Figure 2). For a voxel with partial volume effects, the surroundings will also contribute to the signal and the spiral will be shifted with respect to the origin. When neglecting this shift and just calculating the ΔR_2^* from the total signal of the voxel, both erroneous peaks and under- or overestimation of the concentration of contrast agent can occur (see Fig. 2). However, by an iterative fit of the contribution of the surroundings, it is possible to correct for partial volume effects when the artery is oriented parallel to B_0 (1,8).

Artery not parallel to the main magnetic field

When the artery is not oriented parallel to the main magnetic field, the contrast agent will also affect the magnetic field outside the vessel. This situation occurs for input function measurements in the MCA and for local arterial input function algorithms. The magnetic field changes outside the artery will lead to a far more complicated situation for partial volume voxels, since the contribution of the surroundings of the artery will now depend on the concentration of contrast agent within the artery. The total signal of the voxel will now depend on: radius of the vessel, location of voxel with respect to vessel, angle of the vessel with respect to the main magnetic field, and the size of the voxel. Whether quantitative arterial input function measurements are feasible in arteries oriented at unknown orientation with respect to the main magnetic field, remains to be studied (9).

Local arterial input function measurements

A recent new development is local arterial input function measurements (10). In this approach more

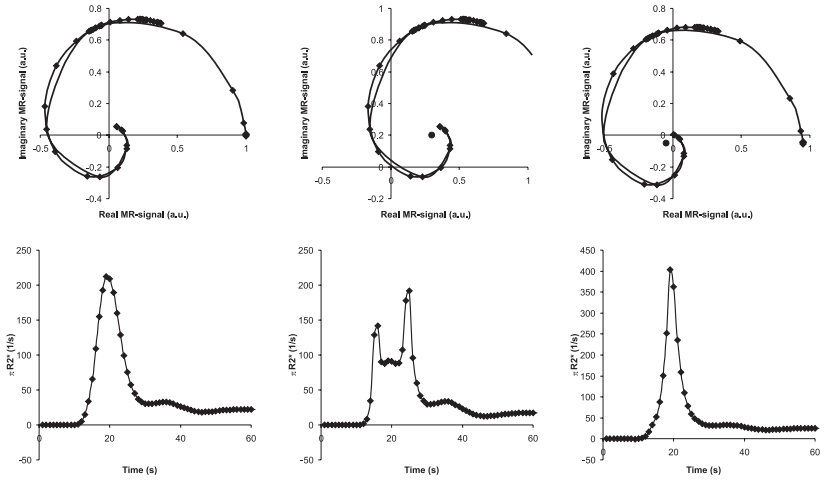

Figure 2: Influence of partial volume effects on the shape of the input function. The dot indicates the contribution of surrounding tissue. Left: pixel exclusively sensitive to blood. Middle: erroneous peaks on the input function. Right: Overestimation of input function.

than one input function per perfusion experiment is used, that is for each voxel an individual input function is defined from arterial structures in its direct environment. Main advantage of the local AIF approach is that the input function measurement is performed much closer to the tissue under investigation and thereby reflects the true input function much better.

Contrast agent properties-tissue

Based on the first articles of Rosen *et al*, all perfusion MR studies have assumed a linear relation between the concentration of contrast agent in tissue and the $\Delta R_2^{(*)}$ (11-14). However, there is only limited evidence for this assumption and the proportionality constant is unknown. Recently, Kiselev has combined many theoretical models to investigate the correctness of this assumption and the influence on perfusion measurements (15). Central in this study is the observation that the extravascular signal traverses both the diffusional narrowing regime (characteristic diffusion length large compared to the field inhomogeneities) and the static dephasing regime (diffusional length much smaller than the field disturbances). This theoretical study reveals potential large errors due to the transitions between the different regimes. Such errors can certainly explain differences between the MR measures of perfusion and other modalities, like PET. However, for clinical practice it will be important to investigate whether these errors show large inter- and intra-patient variation or that these errors could be corrected for by general correction factors. Because these signal formation processes are the basis of perfusion MRI, a solid practical validation of this theoretical study is essential.

Perfusion model/tracer kinetics

For a detailed description of tracer kinetics the reader is referred to basic articles and books on tracer kinitecs and perfusion MRI (16-20). However, to understand quantification issues in perfusion imaging, it is necessary to be aware of some of the basic assumptions and therefore inherent limitations of this technique, namely:

- The contrast agent remains intravascular and extracellular, implying that the contrast agent resides only in blood-plasma. However, the measured plasma-flow is not characteristic for the flow of whole blood as it is known that blood plasma travels at a different velocity than red blood cells do, leading to hematocrit differences between large and small vessels. Therefore, a correction factor is frequently used to correct for these hematocrit differences. This factor is usually assumed constant for all subjects and patients, even though it is known to vary.
- The measured arterial input function is assumed to represent the input function at tissue level. In patients with stenoses or other vascular pathology between the location of the input function measurement and the tissue, the shape of the bolus will change and the measured input function will no longer be representative for the input function of the tissue (21-23). Such dispersion will lead to errors in the calculated perfusion values. A potential solution for this problem is to use a local AIF approach that aims at measuring the input function at tissue level (10,24). However, partial volume effects are known to affect both the shape and the amplitude of such local AIFs and therefore more research has to be performed to verify that this yields correct input function measurements (9).

Injection protocol

To achieve a sharp bolus profile that enables accurate CBF-measurements, fast injection of the contrast agent and the use of a large chaser of saline are essential. By means of simulations, the influence of the injection protocol on calculated perfusion parameters has been investigated (25). For a contrast agent of 500 mM Gd-DTPA at a 1.5 Tesla MRI scanner, an optimal injection speed of 4 – 5 ml/sec was found. Higher injections speeds do not improve CBF quantification because the dispersion of heart and lungs will dominate over the sharper injection profile. Furthermore, for higher rates, the diameter of the cannula for the IV line needs to be larger than the typical 20 gauge, potentially leading to increased patient discomfort. The chaser should be at least 30 ml. Recently, more concentrated contrast agents have been introduced that either can help create a sharper bolus profile using the same injection speed or can enable a lower injection speed.

Deconvolution method

Detailed knowledge about the behaviour of the deconvolution method with respect to different shapes of the residue function, dispersions and delays between input function and tissue passage, and signal to noise is essential for correct interpretation of perfusion data. The original proposed singular value decomposition (SVD) algorithm used for deconvolution , for example, produced results that were fairly

robust to low SNR and were independent with respect to underlying residue function but had a large dependence on delays between the input function and the tissue passage curves, leading to severe errors of the CBF quantification (17,21). However, several deconvolution methods have recently been proposed that are less sensitive to the presence of a delay between the input function and tissue passage (26-28). Therefore, the use of delay sensitive techniques should be discouraged at this moment. Due to differences in implementation of validation methods, it is very difficult to directly compare deconvolution techniques. Furthermore, one should differentiate between methods that provide accurate CBF quantification and methods that describe the shape of the residue function accurately. At the moment, deconvolution techniques that have been adequately characterized encompass SVD, Fourier, and maximum-likelihood expectation maximization (MLEM) methods (29).

Temporal resolution

Two studies have investigated the effect of the sampling rate on the accuracy of CBF measurements (25,30). When the input function and tissue passage curve are sampled too sparsely, deconvolution will result in an underestimation of the maximum value of the residue function and thus an underestimation of the CBF. Interpolation of both curves can somewhat reduce these errors (31). Both studies conclude that the temporal resolution should be higher than 1.5 sec.

Post-processing

When region-of-interest (ROI) values of perfusion parameters are necessary, two different approaches can be chosen:

1. First calculate single pixel maps of the perfusion parameters and average the perfusion parameters over the ROIs
2. Average the tissue passage curves over the ROI and deconvolve this averaged curve with the AIF. From the resulting residue function the perfusion parameters can be calculated.

The first approach has the disadvantage that the deconvolution will be performed on more noisy curves, thereby limiting the accuracy. However, the second approach could introduce erroneous broadening of the passage curve through the brain tissue, due to delay differences over the ROI. This would lead to an underestimation of the CBF.

Conclusions

To achieve absolute quantification several issues need to be addressed whereas the most important issues are:

1. An accurate, quantitative arterial input function measurement close to the tissue under investigation
2. Knowledge of the exact contrast agent properties in the microvasculature and the influence of pathology on these properties
3. High temporal resolution
4. Deconvolution method that allows reliable CBF measurements irrespective of shape of residue function

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